PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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20 NOV. 2003

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	18.11.2003
Applicant's or agent's file reference P1014PC00	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK02/00547	20.08.2002	20.08.2001

Applicant
PHARMEXA A/S et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
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Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P1014PC00	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK02/00547	International filing date *(day/month/year)* 20.08.2002	Priority date *(day/month/year)* 20.08.2001
International Patent Classification (IPC) or both national classification and IPC A61K39/00		
Applicant PHARMEXA A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07.03.2003	18.11.2003
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Hars, J Telephone No. +49 89 2399-7825

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK02/00547

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-99 as originally filed

Claims, Numbers

1-37 filed with telefax on 24.10.2003

Drawings, Sheets

1/2-2/2 as originally filed

Sequence listing part of the description, pages:

1-10, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-23,35

   because:

   ☒ the said international application, or the said claims Nos. 1-23,35 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-37
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-37
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	24-34,36,37
	No:	Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

D1: WO 00 72880 A (SCHENK DALE B ;YEDNOCK TED (US); BARD FREDERIQUE (US); NEURALAB LT) 7 December 2000 (2000-12-07)

D2: WO 01 42306 A (CHAIN BENJAMIN ;MINDSET BIOPHARMACEUTICALS USA (US)) 14 June 2001 (2001-06-14)

D3: WO 99 27944 A (SCHENK DALE B ;ATHENA NEUROSCIENCES INC (US)) 10 June 1999 (1999-06-10) cited in the application

D4: WO 01 62284 A (NIELSEN KLAUS GREGORIUS ;BIRK PETER (DK); JENSEN MARTIN ROLAND (DK) 30 August 2001 (2001-08-30) cited in the application

D5: LEES A ET AL: 'Enhanced immunogenicity of protein-dextran conjugates: I. rapid stimulation of enhanced antibody responses to poorly immunogenic molecules' VACCINE, BUTTERWORTH SCIENTIFIC. GUILDFORD, GB, vol. 12, no. 13, 1994, pages 1160-1166, XP002082853 ISSN: 0264-410X cited in the application

Re Item I

Basis of the report

Claim 1 is not in compliance with Art. 34(2b) PCT, as subject matter was added going beyond the application as filed.
Under a) and c) of present claim 1 the original wording 'the foreign TH epitope' was replaced by 'the at least one foreign TH epitope'.
Although the original claim 1 as filed contains the wording 'at least one foreign TH epitope' in its first paragraph, it is clear that the following, more specific technical choices a)-e) (original claim 1) only refer to 'the foreign TH epitope', narrowing the scope explicitly.

For this report, the original wording 'the foreign TH epitope' was assumed.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-23,35 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The International Search Report contains a document of the P category. Should the applicant envisage to enter the European phase, the subject matter of this document D4 may become pertinent concerning novelty and inventive step.

V.1 INVENTION

Auto-immunisation therapy of Alzheimer's disease with beta-amyloid (APP,Aß) analogues (protein, nucleic acids or microorganisms expressing the latter) containing or linked to a foreign T-Helper epitope (can be a promiscous epitope such as P2 or P30 (from Tetanus toxoid), diphteria toxoid epitope, diphtheria toxoid epitope, influenza virus hemagglutinin epitope, P. falciparumn CS epitope) and optionally to a polyhydroxypolymer.
Disrupted subsequences of APP and Aß are used.
Also claimed is a cell-line transformed with a vector incorporating the nucleic acid coding for the above agent.
The analogues are designed to break the auto-tolerance against APP or Aß so that antibodies are raised against APP or Aß, where the response is preferably directed against the intra-cellular parts of these peptides as to avoid an immune-response against cells expressing the peptides.

V.2 CLARITY

Claims 9 and 10 merely state an underlying problem or a desirable function without indicating technical features that would solve the problem or deliver the function. This renders the corresponding claims unclear (Art. 6 PCT). To overcome this objection, the technical features have to be introduced into the claim.

The following formulations are objected to:

- 'B-cell epitopes which are not exposed to the extracellular phase' (claim 9)
- 'analogue lacks at least one B-cell epitope which is exposed to the extracellular phase' (claim 10)

The skilled person would have difficulties determining which B-cell epitopes are intracellular or extracellular. The application only provides information about the transmembrane region of APP, but not about which part is intarcellular and which extracellular for APP. Further, cell-bound Aß may be inserted differently into the cellular membrane than APP.
Requiring the skilled person to first establish the location of the different parts of APP and Aß and then to determine the B-cell epitopes only to construe the scope of claims 9 and 10 is going too far.

Further, claim 9 refers to an undefined entity: 'the precursor polypeptide Aß.'

The applicant should delete all statements similar to 'incorporated herein by reference'.

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1,D2 is not mentioned in the description, nor are these documents identified therein.

Although claims 1 and 23, 25 and 36 (pairwise) have been drafted as separate independent claims, they appear to relate effectively to the same subject- matter and to differ from each other only with regard to the definition of the subject- matter for which protection is sought and in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of in- dependent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection.

Hence, claims 1 and 24, 26 and 37, do not meet the requirements of Article 6 PCT.

In order to overcome this objection, it would appear appropriate to file an amended set

of claims defining the relevant subject-matter in terms of a minimum number of claims in each category followed by dependent claims covering features which are merely optional (Rule 6.4 PCT).

V.3 PRIOR ART

If not otherwise specified, subject matter of cited documents relates to the passages indicated in the search report.

D1
Synthetic vaccines for the treatment of Alzheimer's comprising one or more (different) B cell epitopes of Abeta (Abeta 1-7 or 3-9, but also up to 20 aas) and one or more (different) promiscous (universal) T helper epitopes (e.g. tetanus or diphtheria toxoid). The fusion peptides can be arranged in all possible linear forms (specific examples given) or even dendritic forms (MAPs: two or more of the fusion peptides are linked separately to a peptidic backbone). The idea is to generate a B cell response against A beta without affecting APP.
The vaccines can be administered in peptide form, as nucleic acids or via viruses/bacteria, together with adjuvants, in a dose of > 10 ug peptides. The linear fusion peptides are produced through standard recombinant technology.

D2
Synthetic peptide vaccines comprising one or several (different) copies of a promiscous (or immunodominant) T helper epitope (e.g. tetanus or diphteria toxoid), a spacer of 0-5 aas (glycine) and a B cell epitope (2-5 aas) of naturally occuring cleavage peptides of beta-APP (e.g. of A beta 40/42/43 or fragments thereof), for the treatment of Alzheimer's disease. The idea is to break autotolerance and raise antibodies against A beta without generating an immune response compromising beta-APP's natural function. The vaccines can be produced by standard DNA/protein technology. The T helper epitope can be lipid-modified. Administration can incur adjuvants, one or multiple doses (unit of 0.5-1000 ug per kg weight), poly(lactide-co-glycolide) microparticles, by oral or parenteral route.
Additionally, a mixture of synthetic peptides with different T helper epitopes can be administered.

D3

A synthetic vaccine to treat Alzheimer's where Abeta 42 (or active fragments) is fused to peptides promoting the immune response against Abeta, e.g. tetanus or diphtheria toxoid. The Abeta part can be present in multiple copies. The fusion peptide can be administered with adjuvants at a dose of at least 1 or 10 ug, or in nucleic acid form, e.g. in a viral vector.

D5
Rapid stimulation of enhanced antibody responses to poorly immunogenic molecules by conjugating the epitope to a dextran.

V.4 NOVELTY

Remarks under Art. 33(2) PCT

None of the cited documents discloses the use of a disrupted APP or Aß sequence. Claims 1-37 therefore appear to be novel according to Art. 33(2) PCT.

V.5 INVENTIVE STEP

Remarks under Art. 33(3) PCT

Document D1, which is considered to represent the most relevant state of the art, discloses a synthetic vaccine comprising a B cell epitope from Aß and a T helper epitope, where these epitopes are fused together and two or more of these fusion peptides can be linked separately to a peptidic backbone, from which the subject-matter of claim 1 differs in that a disrupted APP or Aß sequence is employed so that the analogue does not include any subsequence of SEQ ID NO: 2 that binds productively to MHC class II molecules initiating a T-cell response.
The technical effect achieved in the case of claim 1 is the avoidance of a prolonged autoimmune reaction against Aß or APP, once the vaccine is no longer administered (see page 44, line 29 - page 45, line 16 of the description of the present application). This technical effect is not achieve in the case of D1.
The problem to be solved by the present invention may therefore be regarded as how to provide an enhanced vaccine based on APP or Aß.
The solution proposed in claim 1 of the present application appears to involve an inventive step (Article 33(3) PCT) for the following reasons.
The problem of a prolonged autoimmune reaction after administration of the vaccine was not addressed in D1, neither in the other cited documents. The cited documents all

aim at increasing immunogenicity of the vaccine, whereas the disruption of Aß or APP subsequence decreases the immunogenicity.
The skilled artisan, unaware of this problem of acquired immunity, would not have seeked to reduce the immunogenicity of the vaccine, and in particular he would not have thought of disrupting the APP or Aß subsequence.

15444PCT00

Druckexemplar

CLAIMS

1. A method for *in vivo* down-regulation of amyloid precursor protein (APP) or beta amyloid (Aβ) in an animal, including a human being, the method comprising effecting presentation to the animal's immune system of an immunogenically effective amount of at least one analogue of APP or Aβ that incorporates into the same molecule a substantial fraction of B-cell epitopes of APP and/or Aβ so that the analogue reacts to the same extent as does APP or Aβ with a polyclonal serum raised against APP or Aβ, and at least one foreign T-helper epitope (T_H epitope) so that immunization of the animal with the analogue induces production of antibodies against the animal's autologous APP or Aβ, wherein the analogue

a) is a polyamino acid that contains the at least one foreign T_H epitope and a disrupted APP or Aβ sequence so that the analogue does not include any subsequence of SEQ ID NO: 2 that binds productively to MHC class II molecules initiating a T-cell response; and/or

b) is a conjugate comprising a polyhydroxypolymer backbone to which is separately coupled a polyamino acid as defined in a); and/or

c) is a conjugate comprising a polyhydroxypolymer backbone to which is separately coupled 1) the at least one foreign T_H epitope and 2) a disrupted sequence of APP or Aβ as defined in b).

2. The method according to claim 1, wherein

- at least one first moiety is introduced which effects targeting of the analogue to an antigen presenting cell (APC) or a B-lymphocyte, and/or

- at least one second moiety is introduced which stimulates the immune system, and/or

- at least one third moiety is introduced which optimizes presentation of the analogue to the immune system.

3. The method according to claim 2, wherein the first and/or of the second and/or of the third moiety is/are attached as side groups by covalent or non-covalent binding to suitable chemical groups in the APP or Aβ sequence.

4. The method according to any one of the preceding claims, wherein the analogue comprises a fusion polypeptide.

5. The method according to any one of the preceding claims, wherein the analogue includes duplication of at least one B-cell epitope of APP or Aβ and/or introduction of a hapten.

6. The method according to any one of the preceding claims, wherein the foreign T-cell epitope is immunodominant in the animal.

7. The method according to any one of the preceding claims, wherein the foreign T-cell epitope is promiscuous, such as a foreign T-cell epitope which is selected from a natural promiscuous T-cell epitope and an artificial MHC-II binding peptide sequence.

8. The method according to claim 7, wherein the natural T-cell epitope is selected from a Tetanus toxoid epitope such as P2 or P30, a diphtheria toxoid epitope, an influenza virus hemagluttinin epitope, and a *P. falciparum* CS epitope.

9. The method according to any one of the preceding claims, wherein the analogue comprises B-cell epitopes which are not exposed to the extracellular phase when present in a cell-bound form of the precursor polypeptide Aβ.

10. The method according to any one of the preceding claims, wherein the analogue lacks at least one B-cell epitope which is exposed to the extracellular phase when present in a cell-bound form of the precursor polypeptide.

11. The method according to any one of the preceding claims, wherein the analogue comprises at most 9 consecutive amino acids of SEQ ID NO: 2., such as at most 8, at most 7, at most 6, at most 5, at most 4, and at most 3 consecutive amino acids.

12. The method according to claim 11, wherein the analogue comprises at least one subsequence of SEQ ID NO: 2 so that each such at least one subsequence of SEQ ID NO: 2 independently consists of amino acid stretches selected from the group consisting of 9 consecutive amino acids of SEQ ID NO: 2, 8 consecutive amino acids of SEQ ID NO: 2, 7 consecutive amino acids of SEQ ID NO: 2, 6 consecutive amino acids of SEQ ID NO: 2, 5 consecutive amino acids of SEQ ID NO: 2, 4 consecutive amino acids of SEQ ID NO: 2, and 3 consecutive amino acids of SEQ ID NO: 2.

13. The method according to claim 11 or 12, wherein the consecutive amino acids begin at an amino acid residue selected from the group consisting of residue 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, and 714.

14. The method according to any one of the preceding claims, wherein presentation to the immune system is effected by having at least two copies of an Aβ derived fragment or the analogue covalently or non-covalently linked to a carrier molecule capable of effecting presentation of multiple copies of antigenic determinants.

15. The method according to any one of the preceding claims, variants b) or c), wherein the polyamino acid and T_H epitope are attached to the polyhydroxypolymer by means of an amide bond.

16. The method according to any one of the preceding claims , variants b) or c), wherein the the polyhydroxypolymer is a polysaccharide.

17. The method according to any one of the preceding claims, wherein the analogue has been formulated with an adjuvant which facilitates breaking of autotolerance to autoantigens.

18. The method according to any one of the preceding claims, wherein an effective amount of the analogue is administered to the animal via a route selected from the parenteral route such as the intracutaneous, the subcutaneous, and the intramuscular routes; the peritoneal route; the oral route; the buccal route; the sublinqual route; the epidural route; the spinal route; the anal route; and the intracranial route.

19. The method according to claim 18, wherein the effective amount is between 0.5 µg and 2,000 µg of the analogue.

20. The method according to any one of claims 1-13, variant a), wherein presentation of the analogue to the immune system is effected by introducing nucleic acid(s) encoding the analogue into the animal's cells and thereby obtaining *in vivo* expression by the cells of the nucleic acid(s) introduced.

21. The method according to claim 20, wherein the nucleic acid(s) introduced is/are selected from naked DNA, DNA formulated with charged or uncharged lipids, DNA formulated in liposomes, DNA included in a viral vector, DNA formulated with a transfection-facilitating

protein or polypeptide, DNA formulated with a targeting protein or polypeptide, DNA formulated with Calcium precipitating agents, DNA coupled to an inert carrier molecule, DNA encapsulated in chitin or chitosan, and DNA formulated with an adjuvant.

22. The method according to any one of claims 18-21, which includes at least one administration/introduction per year, such as at least 2, at least 3, at least 4, at least 6, and at least 12 administrations/introductions.

23. The method according to any one of the preceding claims used for treating and/or preventing and/or ameliorating Alzheimer's disease or other diseases and conditions characterized by amyloid deposits, where APP or Aβ is down-regulated to such an extent that the total amount of amyloid is decreased or that the rate of amyloid formation is reduced with clinical significance.

24. An analogue of APP or Aβ which is derived from an animal APP or Aβ wherein is introduced a modification which has as a result that immunization of the animal with the analogue induces production of antibodies against the animal's autologous APP or Aβ, and wherein the analogue is as defined in any one of claims 1-16.

25. An immunogenic composition comprising an immunogenically effective amount of an analogue according to claim 24, the composition further comprising a pharmaceutically and immunologically acceptable carrier and/or vehicle and optionally an adjuvant.

26. A nucleic acid fragment which encodes an analogue according to claim 24.

27. A vector carrying the nucleic acid fragment according to claim 26, such as a vector that is capable of autonomous replication.

28. The vector according to claim 27 which is selected from the group consisting of a plasmid, a phage, a cosmid, a mini-chromosome, and a virus.

29. The vector according to claim 27 or 28, comprising, in the 5'→3' direction and in operable linkage, a promoter for driving expression of the nucleic acid fragment according to claim 26, optionally a nucleic acid sequence encoding a leader peptide enabling secretion of or integration into the membrane of the polypeptide fragment, the nucleic acid fragment according to claim 26, and optionally a terminator.

30. The vector according to any one of claims 27-29 which, when introduced into a host cell, is capable or incapable of being integrated in the host cell genome.

31. The vector according to claim 29 or 30, wherein the promoter drives expression in a eukaryotic cell and/or in a prokaryotic cell.

32. A transformed cell carrying the vector of any one of claims 27-31, such as a transformed cell which is capable of replicating the nucleic acid fragment according to claim 26.

33. The transformed cell according to claim 32, which is a microorganism selected from a bacterium, a yeast, a protozoan, or a cell derived from a multicellular organism selected from a fungus, an insect cell such as an S_2 or an SF cell, a plant cell, and a mammalian cell.

34. The transformed cell according to claim 32 or 33, which expresses the nucleic acid fragment according to claim 27, such as a transformed cell, which secretes or carries on its surface, the analogue according to claim 24.

35. The method according to any one of claims 1-13, variant a), wherein presentation to the immune system is effected by administering a non-pathogenic microorganism or virus which is carrying a nucleic acid fragment which encodes and expresses the analogue.

36. A composition for inducing production of antibodies against amyloid, the composition comprising

- a nucleic acid fragment according to claim 26 or a vector according to any one of claims 27-31, and
- a pharmaceutically and immunologically acceptable carrier and/or vehicle and/or adjuvant.

37. A stable cell line which carries the vector according to any one of claims 7-31 and which expresses the nucleic acid fragment according to claim 26, and which optionally secretes or carries the analogue according to claim 24 on its surface.